PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/011971	22.10.2004	31.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07C67/31, C07C69/675

Applicant
LONZA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/011971

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

1. The following documents (D1-D2) are referred to in this communication :

   D1: EP-A-1 176 135 (TAKASAGO PERFUMERY CO LTD) 30 January 2002
   D2: WO 03/029259 A (DUPRAT DE PAULE SEBASTIEN ; GENET JEAN-PIERRE (FR); DELLIS PHILIPPE (F) 10 April 2003

2. Novelty

   2.1 Document D1 discloses (cf. example 6) a process for the preparation of enantiomerically pure ethyl 4-chloro-3-hydroxybutyrate by ruthenium catalysed asymmetric hydrogenation of the corresponding beta-oxo ester. The chiral ligand used in D1 is structurally similar to the ligand of formula III according to claim 1 with the difference that the difluoromethylene groups are replaced by methylene groups.

   2.2 Document D2 discloses the use of the ligand of formula III according to claim 1 in the asymmetric hydrogenation of 3-oxo butyrates which are structurally different yet very similar to the compounds according to claim 1.

   2.3 The subject-matter of independent claim 1 and dependent claims 2-7 is therefore novel (Article 33(2) PCT).

3. Inventive Step

   3.1 Document D1, related to the production of the same target compounds using a structually similar chiral ligand, is considered to represent the most relevant state of the art.

   The ee achieved in D1 is comparable to that shown in the present examples.

   The problem to be solved by the present invention may therefore be regarded as provision of an alternative process for the preparation of enantiomerically pure 4-halo-3-hydroxybutyrates.

   The solution proposed in claim 1 of the present application cannot be considered

as involving an inventive step (Article 33(2) PCT) for the following reasons :

Document D2 discloses the use of the ligand of formula III according to claim 1 in the asymmetric hydrogenation of 3-oxo butyrates which are structurally very similar to the compounds according to claim 1.

For instance on page 27, table 1, entry 3, the hydrogenation of methyl 3-oxo-butyrate (ee>99 %) and on page 28, table 1, entry 4, the hydrogenation of 4,4,4-trifluoro-3-oxo-butyrate (ee=70 %).

In view of the difference between a trifluoromethyl group and a monochloro methyl group, especially in the electron withdrawing effect, the skilled person would not consider the moderate enantioselectivity achieved for compounds having strongly electron withdrawing perfluoroalkyl groups in D2 as teaching away from the use of a ligand of formula III for the reduction of 4-chloro-3-hydroxybutyrate.

It has to be considered, therefore, as a result of routine work to test alternative ligands, especially those which are structurally similar, such as the ligand of formula III disclosed in D2, in a process according to D1, thereby arriving at a process according to claim 1.

3.2 Dependent claims 2-7 relate to reaction conditions (stabilising ligands, counter ions, solvents and pressure) usually applied in this type of hydrogenation reaction (cf. D1-D2) and do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step.